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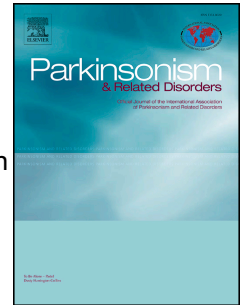
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# Accepted Manuscript

Low adherence to antidepressants is associated with increased mortality in Parkinson disease patients

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**FULL-LENGTH ARTICLE:**

**Low adherence to antidepressants is associated with increased mortality  
in Parkinson disease patients**

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**Key words:** antidepressants, mortality, adherence, anxiety, depression, Parkinson disease

**ABSTRACT**

**Introduction:** The purpose of this study was to evaluate the relationship between adherence to antidepressants (AD) and all-cause mortality in a population-based cohort of patients with Parkinson's Disease (PD).

**Methods:** From a database of more than 4 million people, 8,553 patients with PD who purchased an AD at least once between the years 2008-2011 were retrospectively followed for all-cause mortality over 4-years. Adherence was measured as a ratio between dispensed and prescribed durations and was modeled as: non-adherence (<20%, n=1,566), poor (20%-50%, n=1,184), moderate (50% - 80%, n=1,584), and good (>80%, n=4,219) adherence. Multivariable survival analyses adjusted for demographic and clinical variables including physical comorbidities known to influence mortality were conducted, however there was no adjustment for other psychiatric disorders and medications.

**Results:** Unadjusted mortality rates were 20.4%, 25.1%, 23.4% and 25.6% in those classified as non-adherent, poor, moderate and good adherence respectively ( $\chi^2=18.45$ ,  $p<0.0001$ ). The non-adherent and poor adherence groups had significantly increased adjusted mortality hazard ratios (HR) of 1.43 (CI: 1.26-1.62) and 1.26 (CI: 1.1-1.44) respectively compared to the good adherence group. Using the same model, the adjusted HR for death among males was 1.49 [95% CI: 1.36 – 1.62] compared to females. People with PD and Charlson's Comorbidity Index score of 3-4 (HR 1.3,  $P<0.001$ ) and 5+ (HR 1.78,  $P<0.001$ ) were more likely to die than those with 0-2 comorbidities.

**Conclusions:** Our findings suggest that poor adherence to AD is associated with increased all-cause mortality in people with PD. Given the high prevalence of depression and AD effectiveness, efforts to promote adherence should be prioritized in clinical practice.

## 1. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder, which is associated with considerable reductions in quality of life, morbidity and mortality [1]. Traditionally, PD was defined according to its motor manifestations: tremor, bradykinesia, rigidity and postural instability. It is now considered as a complex condition with additional non-motor symptoms (NMS), such as olfactory dysfunction, pain, sleep behavior disturbances, gastrointestinal symptoms, skin abnormalities and psychiatric disorders [2]. The PRIAMO study [3] found that neuropsychiatric features were the most frequent (67%) NMS, and included, among other, depression, anxiety, hallucinations, apathy, and aggressive behavior.

Depression is considered the most prevalent psychiatric symptom in PD [4,5]. The presence of depressive symptoms is associated with decreased quality of life and less favorable motor outcomes [6,7,8]. It is estimated that up to 50% of patients diagnosed with PD also have depressive symptoms [4,6], and between 10-20% have major depressive disorder (MDD) [9]. Whilst the underlying mechanisms for depression in PD are not fully elucidated, alterations in brain structure, neurotransmitters, and inflammatory and neurotrophic factors all play a role [10]. Moreover, psychosocial factors, higher levels of pain and deterioration in mobility impact on mental health in people with PD [10].

A frontline approach to tackling depression and in particular MDD is Antidepressants (AD) medication. AD are an effective treatment for MDD and within the context of other physical comorbidities [11], including patients with neurologic

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disorders [12]. More recently, there is a growing evidence base for AD use in people with PD [12,13].

Ultimately, AD treatment outcomes are highly influenced by adherence rates [14]. In MDD, low adherence to AD medication has been identified as a risk factor for emergency department visits, hospitalization rates and an increased severity of depression [15]. Medication adherence is known to be variable and low in people with PD and is associated with worse health outcomes and increased financial costs [16].

Surprisingly, the influence of AD adherence on outcomes in people with PD is relatively unknown. In particular, the relationship between antidepressant adherence and mortality is not established. To our knowledge, only one study has investigated AD use and mortality in people with PD [17]. The authors established that people with PD taking selective serotonin reuptake inhibitors (SSRI) and/ or serotonin-noradrenaline re-uptake inhibitors (SNRI) AD were more likely to die than a) people with PD not taking AD medication (Odds ratio (OR) 1.19,  $p=0.01$ ) and b) age and sex matched controls (OR 1.77,  $p<0.01$ ). Whilst this study advanced the field, a number of key limitations persist. First, the authors did not differentiate between rates of AD adherence among their sample. Second, the authors did not consider the impact of pertinent confounders, known to influence mortality, such as the presence of physical comorbidities. Moreover, although they adjust for socioeconomic factors in the selection of patients and controls, they did not adjust for socioeconomic factors in the comparison of survival within PD.

Given the aforementioned gaps and limitations within the literature, our primary objective was to evaluate the association between all-cause mortality rates and adherence to AD among a representative cohort of people with PD from a database covering more

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than 4 million individuals, taking into account important confounders. We hypothesized that lower levels of adherence to antidepressants, would increase an individual's with PD risk of mortality in an inverse dose response manner.

## **2. METHODS**

### **2.1 Population and study period**

Data from the integrated medical records of Clalit Health Services (CHS), the largest health provider in Israel, covering over 4 million subjects (53% of the nation population) was utilized in the current study. The CHS database is described in full in our previous publication [18]. In summary, the database includes demographic information, diagnoses from ambulatory services, family physicians, hospital admissions and specialists, drug prescriptions, laboratory tests and imaging results.

We retrospectively analyzed the entire CHS patient population during the study period (1.1.2008 until 1.1.2012) across all ages (N=4,056,700). We included all patients with at least one prescription for an AD during the study period and a clinical diagnosis of Parkinson's Disease (PD) ICD code G.20 (N=9,884). All Food and Drug Administration (FDA) approved AD were included for the current paper. Extraction was based on the WHO Anatomical Therapeutic Chemical (ATC) code N06A. In the final analyses we included only AD users, specifically patients with PD who purchased at least one prescription (N=8,553). Access to the data warehouse and the analyses were approved for this study by the Clalit Health Services Institutional Review Board.

### **2.2 Measures**

#### *2.2.1 Primary Outcome*

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A record of death from any cause during the four-year study period (produced by the Ministry for Interior Affairs) was the primary study outcome. Patients were followed-up from entry to the study (i.e. prescription of AD) until death or were censored at the end of the study period.

## 2.3 Main predictor

### 2.3.1 Adherence to antidepressants

The adherence to antidepressants measure was modeled on the basis of the concept of medication possession ratio (data comes from CHS pharmacies dispensing) with the addition of physician prescription data (derived from the electronic record), as previously described in detail [19].

Study participation duration was calculated as the continuous period between the first and the last prescribed AD. Adherence was defined as the period of AD **purchased** prescriptions (months), during follow-up, divided by study participation duration (months). Thus it reflects adherence over the period for which AD were known to be prescribed. Adherence was calculated across all AD groups used. Switching between different AD compounds was not taken into account.

$$Adherence (\%) = \frac{\text{Duration of **purchased** AD prescriptions (Months)}}{\text{Duration of continuous **prescribed** AD (Months)}} \times 100$$

Adherence is reported as a percentage score for each patient. Patients with adherence below 20% were considered non-adherent, those with 20%-50% adherence were considered poorly adherent, those with 50%-80% were considered to have a moderate adherence and patients with adherence above 80% were considered to have good



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adherence. The adherence categorization was based on previously published data utilizing this database [20].

#### 2.4 Covariates

We collected the following socio-demographic and clinical variables at study entry: age (categorized into 0-18, 18-24, 24-40, 40-64, 65-74, 75-84, 85+ years), gender and socioeconomic status (based on ecological data). We extracted all available data on physical comorbidities diagnosed by a physician (ICD-10 diagnoses). Based on these data, we calculated the Charlson's Comorbidity Index (CCI), the most widely used clinical index for the evaluation of comorbidities. The CCI weighs twenty chronic conditions as predictors of 1-year relative risk of death, and scores between 1 to 20 [21].

#### **2.5 Analysis**

Statistical analysis was conducted using SPSS version 20 (IBM Corporation, Armonk, New York). We performed descriptive statistics of socio-demographics, co-morbidities, and adherence levels across the total study population as well as across the four adherence level groups. Univariate analyses were used to assess the association between socio-demographics and clinical covariates and those who died or survived during the study period. The multivariable Cox proportional hazard regression model was used to assess the adjusted association between risk of death and adherence level of AD medication controlling for the confounders found to be significant in the univariate analysis (age, gender and physical co-morbidities modeled as CCI). We tested the assumptions of the proportional hazard model using log (-log) plots. Hazard ratios (HR)

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and their 95% confidence interval (95%CI) are reported.  $P < 0.05$  was considered significant. All analyses were two-tailed.

### 3. RESULTS

#### 3.1 Population Characteristics

Population characteristics and mortality rates distributed among variables are shown in Table 1. Briefly, among the 8,553 individuals in the study, almost 80% of the study population was above 65 years old. The most prevalent co-morbidities among the study population were: hypertension (69.8%), diabetes mellitus (32.9%), ischemic heart disease (36.2%) and past stroke (23.3%). The most frequent concomitant drugs used were: statins (65.8%), acetyl-salicylic acid (58.7%), anxiolytics (52.4%), non-steroidal anti-inflammatory drugs (49.7%), anticonvulsants (34.3%) and antipsychotics (29.6%). Males had a significantly higher unadjusted mortality rate versus females (27.9% vs. 21%, respectively,  $\chi^2=56.38$ ,  $p<0.0001$ ). There was no significant difference in mortality according to socioeconomic status. People with higher CCI scores were more likely to die (39.8% on CCI >5 vs. 17.8% on CCI 0-2,  $p<0.0001$ ).

The mean follow-up time of the study period was  $27.6\pm15.6$  months (range 1–47 months, median 30 months). The mean follow-up time of survivors was  $30.7\pm15.2$  months and the mean time to death among those who died was  $17.5\pm12$  months.

#### 3.2 Adherence

Only 9.9% of the study sample discontinued their AD within a month after prescription (i.e. only made a single purchase) and 28.4% of the study sample discontinued the AD within 6 months. The adherence distribution indicated that 18.4% of AD users were non-adherent ( $n=1,566$ ), 13.8% had poor adherence ( $n=1,184$ ), 18.5% had moderate

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adherence (n=1,584) and almost half (49.3%) had good adherence (n=4,219). Unadjusted Mortality rates were: 20.4%, 25.1%, 23.4% and 25.6% in those classified as non-adherent, poor, moderate and good adherence respectively ( $\chi^2=18.45$ ,  $p<0.0001$ ).

### 3.3 Multivariable analysis

The Cox proportional hazards model included mortality as the main outcome and variables significantly associated with mortality in the univariate analyses as covariates.

Adjusted associations between adherence to AD and mortality appear in Table 2.

Using the same model, the adjusted HR for death among males was 1.49 [95% CI: 1.36 – 1.62] compared to females. Patients with CCI score of 3-4 (HR 1.3 [95% CI: 1.17 – 1.44],  $p<0.001$ ) and 5+ (HR 1.78, [95% CI: 1.6 – 1.98],  $p<0.001$ ) were at increased risk of all-cause mortality versus those scoring 0-2. Further adjustment to the use of antipsychotic compound at study entry resulted in HR for mortality 1.35 [95% CI: 1.18 – 1.54] for >80% adherence and HR 1.28 [95% CI: 1.12 – 1.45] for 50%-80% adherence.

## 4. DISCUSSION

The current study found that people who were non-adherent (n=1,566) or had poor adherence (n=1,184) with AD were at elevated risk of mortality by 43% and 26%, respectively, compared to people with PD and good adherence to AD medication (n=4,219). To our knowledge, the current study is the largest to investigate the relationship between antidepressant medication adherence and mortality in people with PD. Moreover, our study is the first to demonstrate the inverse relationship between adherence to these compounds and increased mortality risk, which was only evident after important confounders were considered.

Only one study has previously investigated the impact of AD medication and mortality [17] in PD patients. That study included 510 adults with PD taking SSRI/SNRI medication and established that antidepressant use (classified as a binary variable), was associated with an increased risk of mortality (HR 1.19,  $p=0.01$ ). Whilst helpful, the relatively small sample size, the reliance of AD adherence based upon a binary classification and the fact the authors only adjusted for few confounders (age, sex and medication cessation) are important limitations. Our previous studies have suggested that there is an inverse association between adherence and mortality risk [18,22], a relationship which has been noted in other populations [22]. The unadjusted mortality rates in the current study suggested a linear increased risk in tandem with AD adherence, which at first glance appears to support the previous study by Fransden et al (2016) [17]. However, the strength of our dataset is that we were able to accurately collate information on additional important confounders such as socioeconomic status and physical comorbidities defined according to ICD 10 criteria. Previous research in people with MDD has demonstrated that the relationship between depression and mortality is strongly influenced by the type and number of comorbidities [23]. Within our data set, the univariate analysis demonstrated an incremental increased risk in mortality in people with PD who have more physical comorbidities. This suggests that physical comorbidities play an important role in the increased risk of mortality in those with PD and a factor that we adjusted for in the final model. Within our dataset we found that hypertension (69.8%), diabetes mellitus (32.9%), ischemic heart disease (36.2%) and past stroke (23.3%) were highly prevalent in our representative cohort of people with PD. Cardiovascular diseases are known to be leading causes of premature mortality in the

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general population [24] therefore these results are somewhat expected. Whilst future studies should seek to clarify the precise role of the physical comorbidities and antidepressant adherence on mortality in people with PD, the results from our study demonstrate it is essential that important confounders are considered when attempting to disentangle the relationship between antidepressant medication and mortality in PD. In addition, increasing age was a factor that once adjusted for in the multivariate model was associated with an increased HR for premature mortality among those with lower AD adherence. Again, this is hardly surprising, since this is a relationship commonly observed in the general population.

Given that anxiety and depression are leading contributors to reduced quality of life in people with PD [25] and that antidepressants appear effective in improving depressive symptoms, our data suggest the clinical imperative of encouraging people with PD to be adherent to antidepressant medication. In particular, people who were most adherent to AD medication appear to have the least risk of premature mortality. A recent randomized control trial [26] demonstrated that adherence therapy resulted in improved medication adherence, quality of life, mobility, activities of daily living, emotional wellbeing, cognition, communication, and body discomfort.

In the current study, the mortality HR in PD patients who were non-adherent compared to good adherence was increased by 40%. Interestingly, this magnitude is much higher than the AD effect we previously demonstrated in using similar methodology. In the general population mortality risk increased by 15% [18] while in patients with Ischemic Heart disease it was increased by 13% [22,27]. A possible explanation might be that AD adherence in this specific population might have

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synergistic effect on disease course, combined with anti-parkinsonian drugs. However, at this stage, this is based simply on a hypothesis and clearly more research is required to better elucidate such mechanisms. Such research in the first instance may wish to confirm/ refute our findings regarding adherence and mortality in people with PD.

The exact reasons why non adherence to antidepressant medication is associated with increased mortality is not yet fully elucidated. The association between adherence to AD and survival in PD patients may have several putative mechanisms. Adherence to AD is presumed to reduce depression and anxiety burden and may thus promote adherence to other medications [28]. Since depressive and anxiety disorders are prevalent among PD patients, their symptoms may lead to the aggravation of PD symptoms as well as other co-morbid physical disorders. It is therefore possible that the reduced mortality associated with adherence to AD could be mediated, at least to some extent, via adherence to other life prolonging drugs (such as cardiovascular drugs for example) rather than AD. Another possible explanation that has been proposed is that depression is associated with negative health behavior and therefore AD usage may improve that behavior [29]. AD adherence is presumably associated with more mindful health behaviors (e.g. physical activity, healthy nutrition etc.) which may mediate the link between AD adherence and increased survival. If such, this explanation may also underlie the effect of AD adherence on survival in patients with PD demonstrated in our study. However, these hypotheses remain to be tested in future studies.

Whilst the current study provides novel findings, it is important that the results are interpreted in light of a number of limitations. First, the analyses did not include data regarding the psychiatric diagnoses associated with the need for AD prescription, as

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mental health diagnosis data in the database were incomplete. Second, data on causes of death were also not available, and thus we were unable to discriminate between death due to PD, suicide and other causes. Third, residual confounding by unmeasured variables, such as obesity, mobility limitations and physical inactivity, could have also influenced our findings. Fourth, due to insufficient power we did not stratify the results by AD compound. Future research should seek to explore if the association between AD adherence and mortality in PD differs between different AD medications. Fifth, we did not have information on cognitive impairment and dementia in our sample which may have influenced AD adherence and mortality. Future research may wish to consider the potential impact of cognitive impairment on the relationship between AD adherence and mortality in those with PD. Finally, we did not have a measure of PD disease symptom severity with our sample. Future research should seek to investigate the impact of this on mortality outcomes.

Despite the aforementioned caveats, our study has several key strengths. Our measure of adherence was shown to be reliable [19] and provides important clinical information on the rate of non-adherence. The large sample size (N=8,553) encompassed a nationwide sample of all PD patients who used AD in the CHS database without an age limitation, making it the largest study of its kind. Therefore our findings are generalizable to the general population. Moreover, the Israeli healthcare delivery system is similar to those in other Western countries and thus our findings are also generalizable to these settings. The four-year follow-up period of the present study is long enough to evaluate mortality as an outcome measure, while permitting a large person-time denominator and establishment of causal pathways.



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In conclusion, the present four-year follow-up study is the first to demonstrate the inverse association between adherence to AD and all-cause mortality in a general population-based large cohort of patients with PD (N=8,553) . Even though the standardized effect size of AD may be lower than previously thought [30], the beneficial effect of adherence to AD may be particularly important in the high-risk population of patients with PD. We suggest that neurologists, psychiatrists and primary-care physicians, prioritize the diligent use and efforts to enhance their patients' adherence to AD when indicated, as it may be associated with increased life-expectancy.

## References

- [1] C. H. Dowding, C. L. Shenton, S. S. Salek, A review of the health-related quality of life and economic impact of Parkinson's disease, *Drugs Aging*. 23 (2006) 693-721.
- [2] J. W. Langston, The Parkinson's complex: parkinsonism is just the tip of the iceberg, *Ann. Neurol.* 59 (2006) 591-596.
- [3] P. Barone, A. Antonini, C. Colosimo, R. Marconi, L. Morgante, T. P. Avarello, E. Bottacchi, A. Cannas, G. Ceravolo, R. Ceravolo, G. Cicarelli, R. M. Gaglio, R. M. Giglia, F. Iemolo, M. Manfredi, G. Meco, A. Nicoletti, M. Pederzoli, A. Petrone, A. Pisani, F. E. Pontieri, R. Quatrone, S. Ramat, R. Scala, G. Volpe, S. Zappulla, A. R. Bentivoglio, F. Stocchi, G. Trianni, P. D. Dotto, The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease, *Mov Disord.* 24 (2009) 1641-1649.
- [4] D. Aarsland, J. P. Larsen, N. G. Lim, C. Janvin, K. Karlsen, E. Tandberg, J. L. Cummings, Range of neuropsychiatric disturbances in patients with Parkinson's disease, *J. Neurol. Neurosurg. Psychiatry.* 67 (1999) 492-496.
- [5] S. Grover, M. Somaiya, S. Kumar, A. Avasthi, Psychiatric aspects of Parkinson's disease, *J. Neurosci. Rural. Pract.* 6 (2015) 65-76.
- [6] B. Ravina, R. Camicioli, P. G. Como, L. Marsh, J. Jankovic, D. Weintraub, J. Elm, The impact of depressive symptoms in early Parkinson disease, *Neurology.* 69 (2007) 342-347.
- [7] A. Schrag, M. Jahanshahi, N. Quinn, What contributes to quality of life in patients with Parkinson's disease?, *J. Neurol. Neurosurg. Psychiatry.* 69 (2000) 308-312.
- [8] D. Weintraub, P. J. Moberg, J. E. Duda, I. R. Katz, M. B. Stern, Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease, *J. Am. Geriatr. Soc.* 52 (2004) 784-788.
- [9] E. Tandberg, J. P. Larsen, D. Aarsland, J. L. Cummings, The occurrence of depression in Parkinson's disease. A community-based study, *Arch. Neurol.* 53 (1996) 175-179.
- [10] D. Aarsland, S. Pahlhagen, C. G. Ballard, U. Ehrt, P. Svenningsson, Depression in Parkinson disease--epidemiology, mechanisms and management, *Nat. Rev. Neurol.* 8 (2012) 35-47.
- [11] L. Rayner, A. Price, A. Evans, K. Valsraj, I. J. Higginson, M. Hotopf, Antidepressants for depression in physically ill people, *Cochrane. Database. Syst. Rev.* (2010) CD007503.

- [12] A. Price, L. Rayner, E. Okon-Rocha, A. Evans, K. Valsraj, I. J. Higginson, M. Hotopf, Antidepressants for the treatment of depression in neurological disorders: a systematic review and meta-analysis of randomised controlled trials, *J. Neurol. Neurosurg. Psychiatry*. 82 (2011) 914-923.
- [13] F. L. Rocha, M. G. Murad, B. P. Stumpf, C. Hara, C. Fuzikawa, Antidepressants for depression in Parkinson's disease: systematic review and meta-analysis, *J. Psychopharmacol*. 27 (2013) 417-423.
- [14] J. R. Geddes, S. M. Carney, C. Davies, T. A. Furukawa, D. J. Kupfer, E. Frank, G. M. Goodwin, Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review, *Lancet*. 361 (2003) 653-661.
- [15] S. C. Ho, H. Y. Chong, N. Chaiyakunapruk, B. Tangiisuran, S. A. Jacob, Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review, *J. Affect. Disord*. 193 (2016) 1-10.
- [16] N. Malek, D. G. Grosset, Medication adherence in patients with Parkinson's disease, *CNS. Drugs*. 29 (2015) 47-53.
- [17] R. Frandsen, L. Baandrup, J. Kjellberg, R. Ibsen, P. Jennum, Increased all-cause mortality with psychotropic medication in Parkinson's disease and controls: a national register-based study, *Parkinsonism. Relat Disord*. 20 (2014) 1124-1128.
- [18] A. Krivoy, R. D. Balicer, B. Feldman, M. Hoshen, G. Zalsman, A. Weizman, G. Shoval, Adherence to antidepressants is associated with lower mortality: a 4-year population-based cohort study, *J. Clin. Psychiatry*. 77 (2016) e566-e572.
- [19] S. R. Singer, M. Hoshen, E. Shadmi, M. Leibowitz, N. Flaks-Manov, H. Bitterman, R. D. Balicer, EMR-based medication adherence metric markedly enhances identification of nonadherent patients, *Am. J. Manag. Care*. 18 (2012) e372-e377.
- [20] S. Karve, M. A. Cleves, M. Helm, T. J. Hudson, D. S. West, B. C. Martin, Good and poor adherence: optimal cut-point for adherence measures using administrative claims data, *Curr. Med. Res. Opin*. 25 (2009) 2303-2310.
- [21] M. E. Charlson, P. Pompei, K. L. Ales, C. R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, *J. Chronic. Dis*. 40 (1987) 373-383.
- [22] A. Krivoy, R. D. Balicer, B. Feldman, M. Hoshen, G. Zalsman, A. Weizman, G. Shoval, Adherence to antidepressant therapy and mortality rates in ischaemic heart disease: cohort study, *Br. J. Psychiatry*. 206 (2015) 297-301.
- [23] O. P. Almeida, H. Alfonso, G. J. Hankey, L. Flicker, Depression, antidepressant use and mortality in later life: the Health In Men Study, *PLoS. One*. 5 (2010) e11266.

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- [24] S. Yusuf, S. Reddy, S. Ounpuu, S. Anand, Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization, *Circulation*. 104 (2001) 2746-2753.
- [25] S. E. Soh, M. E. Morris, J. L. McGinley, Determinants of health-related quality of life in Parkinson's disease: a systematic review, *Parkinsonism. Relat Disord*. 17 (2011) 1-9.
- [26] D. J. Daley, K. H. Deane, R. J. Gray, A. B. Clark, M. Pfeil, K. Sabanathan, P. F. Worth, P. K. Myint, Adherence therapy improves medication adherence and quality of life in people with Parkinson's disease: a randomised controlled trial, *Int. J. Clin. Pract*. 68 (2014) 963-971.
- [27] V. M. Hunot, R. Horne, M. N. Leese, R. C. Churchill, A cohort study of adherence to antidepressants in primary care: the influence of antidepressant concerns and treatment preferences, *Prim. Care Companion. J. Clin. Psychiatry*. 9 (2007) 91-99.
- [28] A. H. Glassman, J. T. Bigger, Jr., M. Gaffney, Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: seven-year follow-up of SADHART participants, *Arch. Gen. Psychiatry*. 66 (2009) 1022-1029.
- [29] J. Burnett, J. H. Coverdale, S. Pickens, C. B. Dyer, What is the association between self-neglect, depressive symptoms and untreated medical conditions?, *J. Elder. Abuse Negl*. 18 (2006) 25-34.
- [30] K. N. Fountoulakis, A. A. Veroniki, M. Siamouli, H. J. Moller, No role for initial severity on the efficacy of antidepressants: results of a multi-meta-analysis, *Ann. Gen. Psychiatry*. 12 (2013) 26.

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Table 1: Total patients with Parkinson's disease population (N=8,553) characteristics and mortality rates across demographic and clinical variables.

		Population		Mortality	
		N	%	N	%
<b>Total</b>		<b>8,553</b>		<b>2,068</b>	<b>24.2</b>
Gender	Males	3,957	46.3	1,105	27.9*
	Females	4,596	53.7	963	21
Age at study entry	18-24	5	0.0	0	0.0
	25-44	324	3.8	6	1.9
	45-64	1,449	16.9	104	7.2
	65-74	1,743	20.4	269	15.4
	75-84	3,573	41.8	1,009	28.2
	>85	1,459	17.1	680	32.9
Socio-economic status	Low	2,742	32.1	637	23.2
	Moderate	3,659	42.9	879	24
	High	2,128	25	542	25.5
CCI	0-2	5,198	60	913	17.8
	3-4	1,948	22.8	570	29.3*
	>5	1,470	17.2	585	39.8*

\*P<0.05

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Table 2: Hazard ratios (HR) for mortality using Cox regression survival analysis by antidepressants adherence category among patients with Parkinson's disease

Adherence category	Crude	Adjusted 1	Adjusted 2
<0.2	<b>1.24 (1.1-1.4)</b>	<b>1.41 (1.24-1.6)</b>	<b>1.43 (1.26-1.62)</b>
0.2-0.5	<b>1.22 (1.07-1.38)</b>	<b>1.26 (1.1-1.43)</b>	<b>1.26 (1.1-1.44)</b>
0.5-0.8	0.96 (0.86-1.08)	1 (0.9-1.13)	1.02 (0.9-1.15)
>0.8 (Ref.)	1	1	1

Bold=  $p < 0.05$

Adjusted 1: Gender and Age (HR males vs. females: 1.49 (1.36-1.62))

Adjusted 2: Gender, Age and Charlson's Comorbidity Index

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Conflict of interest:

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Authors contributions:

Gal Shoval: contributed to design and conceptualization of the study, analysis and interpretation of the data, and drafting/revising the manuscript for intellectual content

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**Highlights:**

- Depression is common in Parkinson's Disease (PD)
- The beneficial effect of antidepressants may be particularly important in PD
- Poor adherence to antidepressants is associated with a 26%-43% increased mortality
- Promoting antidepressant drug adherence should be a top clinical priority in PD